Remarks

Claims 1-56 are pending upon entry of the foregoing amendments.

Amendments to the Claims

Claims 1, 3, 31, 32, 33, 46, and 50 have been amended to specify that the microparticles have both a geometric size between 0.1 μm and 5 μm and an average porosity between 15 % and 90 % by volume. Support for these amendments can be found explicitly in the specification, for example, at page 11, lines 5-6, and page 12, line 27 through page 13, line 14.

Claims 1, 33, 46, and 50 also have been amended to specify that a particular *combination* of the pharmaceutical agent, matrix material, geometric size, and average porosity for the microparticles is selected to provide that upon inhalation of the formulation into the lungs a therapeutically or prophylactically effective amount of the pharmaceutical agent is released from the microparticles in the lungs for at least 2 hours. Claims 3 and 31 have been amended to specify that the combination of the pharmaceutical agent, matrix material, geometric size, and average porosity are selected to provide that upon inhalation of the formulation into the lungs a majority of the pharmaceutical agent is released no earlier than about 2 hours and no later than about 24 hours following inhalation. Claim 32 has been amended to specify that *the combination* of the pharmaceutical agent, matrix material, geometric size, and average porosity are selected to provide that upon inhalation of the formulation into the lungs there is an increase in MAT_{inh} of at least 25% compared to the MAT_{inh} obtained when the pharmaceutical agent is administered by inhalation of microparticles not in the form of porous microparticles which comprise the pharmaceutical agent and the matrix material. Support for these amendments is

found in the specification, for example, at page 8, lines 11-15; page 9, lines 11-12; and page 10, lines 13-24.

Claim 4 has been amended to specify that the microparticles have a geometric size between 1.7 μm and 3.8 μm. Support for this amendment is found in the specification in Tables 1 and 3 of the examples. Claim 6 has been amended to specify that the microparticles have an average porosity between 28 % and 81 % by volume. Support for this amendment is found in the specification in Tables 1 and 3 of the examples. Claim 5 has been amended to specify that the matrix material is present in an amount between 50 wt. % and 90 wt. %. Support for this amendment is found in the specification at page 13, lines 27-28.

Claim 13 has been amended to specify that the antecedent basis of the term "the polymer" is found in claim 10 as "a biocompatible synthetic polymer." Support for this amendment is found in the specification at page 3, lines 28-29.

Rejection under 35 U.S.C. § 112

Claim 13 was rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. The rejection is respectfully traversed as moot.

Claim 13 has been amended to depend from claim 10 instead of claim 1. As amended, the limitation "the polymer" finds an antecedent basis in claim 10 as "a biocompatible synthetic polymer." The rejection therefore should be withdrawn.

Rejection under 35 U.S.C. § 102

Claims 1-7, 10-12, 14-21, 27, 30, 32-36, 38-48, and 50-53 are rejected under 35 U.S.C. 102(a) as anticipated by U.S. Patent No. 6,436,443 to Edwards et al. (hereinafter "Edwards"). Claims 1-11, 14-35, and 37-56 are rejected under 35 U.S.C. 102(e) as anticipated by U.S. Patent

No. 6,395,300 to Straub et al. (hereinafter "Straub"). The rejection is respectfully traversed if applied to the claims as amended.

Applicants' Claimed Methods and Compositions

Applicants' claimed methods and pharmaceutical formulations provide *sustained* release from microparticles delivered to the lung. The microparticles have a geometric size between 0.1 μm and 5 μm, and an average porosity between 15 % and 90 % by volume.

Furthermore, Applicants' claims require that the microparticles have a selected *combination* of pharmaceutical agent, matrix material, geometric size, and average porosity to provide that a therapeutically or prophylactically effective amount of the pharmaceutical agent is released from the microparticles in the lungs for at least 2 hours. In preferred embodiments, the microparticles provide that the majority of the pharmaceutical agent is released from the microparticles before the microparticles can be removed by pulmonary clearance mechanisms.

Edwards

Edwards discloses particles for drug delivery to the lung, Edwards teaches that "the preferred diameter for porous particles for inhalation therapy is **greater than 5 μm**" (Column 4, lines 17-19) (emphasis added). Edwards fails to disclose microparticles having a geometric size between 0.1 μm and 5 μm. Edwards also fails disclose microparticles having an average porosity between 15 % and 90 % by volume. Accordingly, Applicants' claims as amended clearly are novel over Edwards.

Furthermore, Edwards does not disclose microparticles wherein the *combination* of the pharmaceutical agent, matrix material, geometric size, and average porosity are selected to

provide that upon inhalation of the formulation into the lungs a therapeutically or prophylactically effective amount of the pharmaceutical agent is released from the microparticles in the lungs for at least 2 hours. The examiner alleges without any support that this feature is inherent in Edwards. It is not. A claim element is not "inherent" in the disclosure of a prior art reference unless extrinsic evidence clearly shows that missing descriptive matter is **necessarily** present in the thing described in the reference. In re Robertson, 49 U.S.P.Q. 1949 (Fed. Cir. 1999). "Inherency, however, may not be established by mere probabilities or possibilities" (49 U.S.P.Q. at 1950-51).

This claim feature is structural and compositional described in functional terms, as Applicants' teach that "[f]or a given microparticle composition (pharmaceutical agent and matrix material) and structure (microparticle porosity and thus density) an *iterative process* can be used to define where the microparticles go in the lung and the duration over which the microparticles release the pharmaceutical agent" (page 10, lines 13-16). That process is described at page 9, Line11 to Page 10, Line 29. In contrast, Edwards does not disclose or enable how to select *in combination* a microparticle composition and structure to provide Applicant's claim feature defining the sustained release characteristics of the microparticles.

In addition, Edwards clearly does not suggest Applicants' claimed formulations and methods. In fact, one of ordinary skill in the art would have been led away from making microparticles having a geometric size less than 5 μm, because Edwards teaches

> "[t]he use of larger porous particles is advantageous since they are able to aerosolize more efficiently that smaller, non-porous aerosols such as those currently used for inhalation therapies. The large (>5 μm) porous particles are

also advantageous in that they can more successfully avoid phagocytic engulfment, in comparison to smaller non-porous particles"

(Column 3, lines 58-65). Edwards thus explicitly teaches away from using microparticles having a geometric size between 0.1 μm and 5 μm, as required by Applicants' claims.

In sum, Applicants' claims are clearly novel and non-obvious over Edwards.

Straub

Straub does not disclose microparticles having an average porosity between 15 % and 90 % by volume. Furthermore, Straub does not disclose microparticles wherein the *combination* of the pharmaceutical agent, matrix material, geometric size, and average porosity are selected to provide that upon inhalation of the formulation into the lungs a therapeutically or prophylactically effective amount of the pharmaceutical agent is released from the microparticles in the lungs for at least 2 hours. This claim feature is not a necessary, and thus not an inherent, feature of the compositions described in Straub.

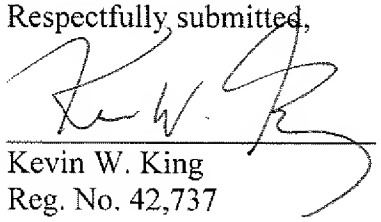
Accordingly, Applicants' claims as amended clearly are patentable over Straub.

Conclusions

For the foregoing reasons, applicants submit that the claims are novel and nonobvious over the prior art of record. Allowance of claims 1-56 is therefore respectfully solicited.

The undersigned respectfully invites the Examiner to contact him by telephone (404.853.8068) if any outstanding issues can be resolved by conference or examiner's amendment.

Respectfully submitted,



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